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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/163,089	09/29/1998	IAN F. C. MCKENZIE	5036-1	9586

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/163,089	MCKENZIE ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 2-13-2006 are acknowledged. Claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 have been canceled. Claims 73-90 have been added. Claims 73-90 are pending and currently under examination.

The Declaration filed on 2-13-2006 has been fully considered.

Claim Rejections Withdrawn

The rejection of claims 1, 3, 5-11, 13-17, 19-21, 24-26, 38 and 70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunoregulatory compositions comprising mannose receptor bearing antigen presenting cells (i.e. macrophages and dendritic cells) and a conjugate comprising tumor antigens MUC1 and CRIPTO and a carbohydrate polymer comprising mannose, wherein said carbohydrate polymer is a fully oxidized carbohydrate polymer comprising free aldehydes, does not reasonably provide enablement for immunoregulatory compositions comprising any mannose bearing cells other than APCs and a conjugate comprising any tumor antigen other than MUC1 and CRIPTO and a carbohydrate polymer comprising mannose, wherein said carbohydrate polymer is a fully oxidized polymer comprising free aldehydes is withdrawn. Cancellation of said claims has rendered the rejection moot. Moreover, this rejection is not being applied to the newly filed claims as they are limited to mannose receptor-bearing antigen presenting cells and in light of Applicant's argument (supported by the Declaration by Dr. Chris Schmidt) that the CTL activation is a function of the carbohydrate polymer not the antigen. An enablement rejection

encompassing the claims not affected by said amendments or the aforementioned arguments is set forth below.

The rejection of claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70 are rejected under 35 U.S.C. 1O3(a) as being unpatentable over McKenzie et al. (EP 0 659 768 A2) in view of Koning et al. (WO 98/13378) is withdrawn. Cancellation of said claims has rendered the rejection moot. The cited art is not being applied to the newly added claims as Applicant's argument that U.S. Provisional Application No. 60/060,594 provides support for the newly added claims and therefore Koning et al. is not available as prior art under 35 U.S.C. 103.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 73-90 are rejected under 35 U.S.C. 1O3(a) as being unpatentable over McKenzie et al. (EP 0 659 768 A2) in view of Maraskovsky et al. (U.S. Patent 6,017,527) for essentially the reasons set forth in the previous Office action in the rejection of claims 1, 3-11, 13-17, 19-21, 24-26, 38 and 70.

The instant claims are drawn to immunoregulatory compositions comprising mannose receptor-bearing antigen presenting cells and a conjugate comprising a tumor antigen (MUCI) and a carbohydrate polymer (fully oxidized mannose).

Applicant argues:

1. Applicant is entitled to a priority date of September 27, 1997.

2. The combination of references does not render the instant invention obvious.

3. There is no teaching or suggestion in McKenzie et al. that it would be desirable to increase the immunogenicity of the antigen conjugate via *ex vivo* pulsing because the said antigen composition is itself a means of increasing antigen immunogenicity.

4. Maraskovsky requires contacting dendritic cells with CD40L after providing the cells with the antigen.

5. The possibility to recombinantly express the antigen conjugated to a carbohydrate polymer with fully oxidized mannose in a dendritic cell.

6. Maraskovsky only envisions antigen that has been purified or partially purified.

7. There is no basis in either reference to put the antigen conjugate of McKenzie et al. into the dendritic cell of Maraskovsky. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination (*In re Mills*).

8. The advantages of pulsing dendritic cells with the recited antigen conjugate (i.e. protection from naturally occurring anti-tumor antibodies) were not known prior to the instant invention.

9. It was unknown prior to the instant invention that the priming of APCs with the recited antigen conjugate caused dendritic cell maturation in the absence of exogenous factors (i.e. CD40L) and the preferential processing of the antigen via the class I pathway (CTL responses).

10. With regard to the enhancement of cellular immunity, from the viewpoint of McKenzie et al., the direct administration of the conjugate was already effective in inducing cellular immunity and they were unaware of the advantage to be afforded by protecting said conjugate from natural antibodies. Moreover, Maraskovsky et al. does not teach or suggest these advantages since Maraskovsky et al. does not modify the antigen presentation by the cell.

11. One could not predict that the combination of the cited teachings would provide an advantage over the specific immune-response enhancing solution of McKenzie et al alone or Maraskovsky et al. alone.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, both McKenzie et al. and Maraskovsky et al. are available as prior art under 35 U.S.C. 103 even when Applicant is afforded the priority date of September 27, 1997.

With regard to Points 3 and 7, Maraskovsky et al. not McKenzie et al. provide the motivation to combine the cited references in that *ex vivo* pulsing of dendritic cells enhances the antigen presenting capacity of the dendritic cells (see column 1, lines 52-56) hence increasing the immunogenicity of the antigen (and thereby reducing the amount of antigen required to induce a given immune response in an subject).

With regard to Point 4, the instant claims do not preclude dendritic cell activation by CD40L. The instant claims merely require a composition comprising mannose receptor bearing APCs that have been *in vivo* or *ex vivo* pulsed with a carbohydrate polymer comprising mannose wherein said polymer is a fully oxidized carbohydrate polymer comprising free aldehydes.

With regard to Point 5, applicant's argument are predicated on the fact that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the antigen conjugated to the recited carbohydrate polymer is recombinantly expressed in dendritic cells) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to Point 6, Maraskovsky et al. is not limited to use of purified or partially purified antigens. Maraskovsky et al. can utilize any antigen that can be processed by dendritic cells (see column 5, lines 21-26 and column 10, line 27 to column 11, line 3). As McKenzie et al. disclose that the claimed conjugate stimulates a cellular response (which requires processing by an APC); said conjugate would meet the definition of an antigen as set forth by Maraskovsky et al.

With regard to Points 8-10, whether the advantages provided by the instant invention (i.e. protection from natural antibodies etc.) where known prior to the instant invention is not germane as said advantages were not the motivation to combine cited references. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

With regard to Points 2 and 11, McKenzie et al. disclose a conjugate comprising a tumor antigen (mucin) and a carbohydrate polymer (mannose) that is used to induce cell-mediated immune responses (see abstract). McKenzie et al further disclose a conjugate which consists of the MUCI antigen and a fully oxidized mannose polymer (see pate 4, lines 19-20); the use of immune regulators such as GM-CSF, IL-3, and IL-4 (see page 5, lines 30-34); and that the antigen comprise repeating subunits of at least 5 amino acids (see page 3, lines 1-3).

McKenzie et al. differs from the instant claims in that the claimed conjugate is not combined with mannose receptor-bearing cells at the time of administration to the patient or used for the *ex vivo* pulsing of the mannose receptor-bearing cells.

Maraskovsky et al. the use of antigen expressing, activated mannose receptor-bearing cells (dendritic cells) to present tumor antigens to T cells. Moreover, Maraskovsky et al. disclose the use of cytokines in separate, sequential or simultaneous combinations with said activated cells (see abstract). Finally, Maraskovsky et al. disclose methods of inducing specific immune responses utilizing "antigen-pulsed" dendritic cells (see column 11).

Consequently, it would have been obvious for one of skill in the art to combine the antigen-mannose conjugate disclosed by McKenzie et al. with the activated dendritic (mannose receptor bearing) cells as disclosed by Maraskovsky et al. in order to take advantage of the ability of dendritic cells to increase the immunogenicity of antigens (i.e. reduce the amount of antigen needed to induce a given immune response).

One would have had a high expectation of success since Maraskovsky et al disclose since activated dendritic cells can serve as effective agents for enhancing and targeting immune responses to tumor antigens (see column 1, lines 15-47).

New Grounds of Rejection

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 84 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunoregulatory compositions comprising mannose receptor-bearing antigen presenting cells and a conjugate comprising a tumor antigen (MUCI) and a carbohydrate polymer (fully oxidized mannose), does not reasonably provide enablement for said compositions wherein the mannose is a conformational and configurational isomer of mannose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. While Applicant's arguments regarding the ability of an antigen conjugate comprising fully oxidized mannose to elicit a CTL response have been deemed to be persuasive, said arguments do not apply to isomers of mannose. The specification is silent as to the claimed efficacy for compositions comprising a conformational and configurational isomer of mannose.

Moreover, the rejected claims are drawn to compositions that are to be applied to animals/humans. People of skill in the art require documented evidence, that a benefit can be derived by the therapeutic application of a given substance. The specification provides ample evidence those compositions comprising mannose receptor-bearing antigen presenting cells (macrophages) and a conjugate comprising MUC1 and fully oxidized mannose polymer (Ox-M-FP) can be used to elicit a cytotoxic T cell response to MUCI. Moreover, the declaration filed

10-27-2004 demonstrates the efficacy of dendritic cells and a conjugate comprising CRIPTO and fully oxidized mannose polymer for eliciting a cytotoxic T cell response to CRIPTO. However, the instant specification fails to provide direction on what conformation and configurational isomers of mannose are capable of eliciting the claimed immune response. Applicant has failed to give direction on what isomers would meet the limitations of the instant claims and has provided no evidence the application of the any compositions other than those outlined above would elicit the requisite immune response. Given the lack of success in the art, the lack of working examples, and the unpredictability of the generation of a therapeutic response in a living organism, the specification, as filed, is not enabling for the use of antigen conjugates comprising conformational and configurational isomers of mannose to elicit a cellular immune response.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ROBERT ZEMAN
PATENT EXAMINER

May 11, 2006